COMPOUNDS AND METHODS FOR KINASE MODULATION, AND INDICATIONS THEREFOR

This application is a continuation of U.S. application Ser. No. 13/926,959, filed Jun. 25, 2013, which is a continuation application of U.S. application Ser. No. 13/866,353, filed Apr. 19, 2013, which is a continuation application of Ser. No. 12/669,450, filed Jan. 15, 2010, which application is a National Phase application under 35 U.S.C. §371 of PCT/US2008/070124, filed Jul. 16, 2008, which claims the benefit under 35 U.S.C. §119(e) from U.S. Application No. 60/959,907, filed Jul. 17, 2007, which applications are hereby incorporated by reference in their entirety.

FIELD OF THE INVENTION

Background of the Invention

The present invention relates to kinases and compounds which modulate kinases, and uses therefor. Particular embodiments contemplate disease indications which are amenable to treatment by modulation of kinase activity by the compounds of the present invention.

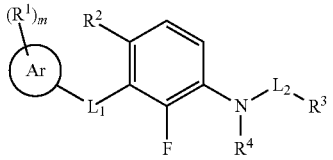
SUMMARY OF THE INVENTION

Compounds are contemplated that are active on protein kinases in general, including, but not limited to, Ab1, Akt1, Akt2, Akt3, ALK, Alk5, A-Raf, B-Raf, Brk, Btk, Cdk2, CDK4, CDK5, CDK6, CHK1, c-Raf-1, Csk, EGFR, EphA1, EphA2, EphB2, EphB4, Erk2, Fak, FGFR1, FGFR2, FGFR3, FGFR4, Flt1, Flt3, Flt4, Fms, Frk, Fyn, Gsk3α, Gsk3β, HCK, Her2/Erbb2, Her4/Erbb4, IGF1R, IKK beta, Irak4, Itk, Jak1, Jak2, Jak3, Jnk1, Jnk2, Jnk3, Kdr, Kit, Lck, Lyn, MAP2K1, MAP2K2, MAP4K4, MAPKAPK2, Met, Mnk1, MLK1, p38, PDGFRA, PDGFRB, PDPK1, Pim1, Pim2, Pim3, PKC alpha, PKC beta, PKC theta, Plk1, Pyk2, Ret, ROCK1, ROCK2, Ron, Src, Stk6, Syk, TEC, Tie2, TrkA, TrkB, Yes, and/or Zap70, including any mutations of these kinases. In some aspects, the compounds are active on Raf protein kinases including A-Raf, B-Raf and/or c-Raf-1, including any mutations thereof. In some aspects, compounds are of Formula I as described below.

Also contemplated in accordance with the present invention are methods for the use of the above-described compounds in treating diseases and conditions associated with regulation of the activity of the above-described kinases. Thus, the use of compounds for therapeutic methods involving modulation of protein kinases are provided, as well as compounds that can be used for therapeutic methods involving modulation of protein kinases.

In some embodiments, compounds have the structure according to the following Formula I:

Formula I



or a salt, a prodrug, a tautomer or an isomer thereof, wherein:

Ar is optionally substituted heteroaryl;

R^1 at each occurrence is independently selected from the group consisting of halogen, optionally substituted lower alkyl, optionally substituted lower alkenyl, optionally substituted lower alkynyl, optionally substituted cycloalkyl, optionally substituted heterocycloalkyl, optionally substituted aryl, optionally substituted heteroaryl, $—NO_2$, —CN, —O—R^5, —N(R^5)—R^6, —C(X)—N(R^5)—R^6, —C(X)—R^7, —S(O)$_2$—N(R^5)—R^6, —S(O)$_n$—R^7, —O—C(X)—R^7, —C(X)—O—R^5, —C(NH)—N(R^8)—R^9, —N(R^5)—C(X)—R^7, —N(R^5)—S(O)$_2$—R^7, —N(R^5)—C(X)—N(R^5)—R^6, and —N(R^5)—S(O)$_2$—N(R^5)—R^6;

m is 0, 1, 2, 3, 4 or 5;

n is 0, 1 or 2;

R^2 is hydrogen, lower alkyl or halogen;

L_2 is selected from the group consisting of —S(O)$_2$—, —C(X)—, —C(X)—N(R^{10})—, and —S(O)$_2$—N(R^{10})—;

R^3 is optionally substituted lower alkyl, optionally substituted C_{3-6} cycloalkyl, optionally substituted heterocycloalkyl, optionally substituted aryl or optionally substituted heteroaryl;

L_1 is selected from the group consisting of a bond, —N(R^{11})—, —O—, —S—, —C(X)—, —C($R^{12}R^{13}$)—X—, —X—C($R^{12}R^{13}$)—, —C($R^{12}R^{13}$)—N(R^{11})—, —N(R^{11})—C($R^{12}R^{13}$)—, —O—C(X)—, —C(X)—O—, —C(X)—N(R^{11})—, —N(R^{11})—C(X)—, —S(O)—, —S(O)$_2$—, —S(O)$_2$—N(R^{11})—, —N(R^{11})—S(O)$_2$—, —C(NH)—N(R^{11})—, —N(R^{11})—C(NH)—, —N(R^{11})—C(X)—N(R^{11})—, and —N(R^{11})—S(O)$_2$—N(R^{11})—;

X is O or S;

R^4, R^{10} and each R^{11} are independently hydrogen or lower alkyl, wherein lower alkyl is optionally substituted with one or more substituents selected from the group consisting of fluoro, —OH, $—NH_2$, lower alkoxy, fluoro substituted lower alkoxy, lower alkylthio, fluoro substituted lower alkylthio, mono-alkylamino, fluoro substituted mono-alkylamino, di-alkylamino, fluoro substituted di-alkylamino, and —$NR^{14}R^{15}$;

R^5, R^6, R^8, and R^9 at each occurrence are independently selected from the group consisting of hydrogen, optionally substituted lower alkyl, optionally substituted C_{3-6} alkenyl, optionally substituted C_{3-6} alkynyl, optionally substituted cycloalkyl, optionally substituted heterocycloalkyl, optionally substituted aryl, and optionally substituted heteroaryl, or

R^8 and R^9 combine with the nitrogen to which they are attached to form a 5-7 membered optionally substituted nitrogen containing heterocycloalkyl or a 5 or 7 membered optionally substituted nitrogen containing heteroaryl;

R^7 at each occurrence is independently selected from the group consisting of optionally substituted lower alkyl, optionally substituted C_{3-6} alkenyl, optionally substituted C_{3-6} alkynyl, optionally substituted cycloalkyl, optionally substituted heterocycloalkyl, optionally substituted aryl, and optionally substituted heteroaryl;

R^{12} and R^{13} are independently selected from the group consisting of hydrogen, fluoro, —OH, $—NH_2$, lower alkyl, lower alkoxy, lower alklylthio, mono-alkylamino, di-alkylamino, and —$NR^{14}R^{15}$, wherein the alkyl chain(s) of lower alkyl, lower alkoxy, lower alkylthio, mono-alkylamino, or di-alkylamino are optionally substituted with one or more substituents selected from the group consisting of fluoro, —OH, $—NH_2$, lower alkoxy, fluoro substituted lower alkoxy,